Eurasian Journal
of Veterinary Sciences

www.eurasianjvetsci.org

RESEARCH ARTICLE

Investigation of the efficacy of tyrosol on doxorubicin-induced acute cardiotoxicity in rats

Mustafa Cellat[1*], Muhammed Etyemez[1]

[1]Hatay Mustafa Kemal University, Veterinary Faculty, Department of Physiology, Hatay, Turkey

Received:08.04.2022, Accepted: 25.07.2022
*mcellat@mku.edu.tr

Ratlarda doksorubusin ile oluşturulan akut kardiyotoksisite üzerine tyrosolün etkinliğinin araştırılması

Eurasian J Vet Sci, 2022, 38, 3, 159-167
10.15312/EurasianJVetSci.2022.378

Öz

Amaç: Çalışmada, doksorubisin ile oluşturulan kardiyotoksisite üzerine tirozolün etkinliğinin araştırılması amaçlandı.

Gereç ve Yöntem: Ratlar 4 gruba ayrıldı ve her grupta 8 rat yer aldı. Grup 1 ve grup 2'ye 1 ml serum fizyolojik, grup 3 ve grup 4'e ise 20 mg/kg dozda tirozol uygulaması yapıldı. Serum fizyolojik ve tirozol uygulamalarında oral gavaj yöntemi kullanıldı. Ayrıca grup 2 ve grup 4'e denemenin 12. günü 15 mg/kg dozda ve tek doz intraperitoneal doksorubisin uygulaması yapıldı. Denemenin 14. gününde anestezi altındaki ratlardan serum ve doku örnekleri alındı ve daha sonra ötanazi edildi. Serum kreatin kinaz MB ve kreatin kinaz aktiviteleri analiz edildi. Kalp dokuları çıkarıldı ve bu dokularda histopatolojik ve oksidatif stres parametrelerine yönelik analizler yapıldı. Kalp dokusu malondialdehit ve redükte glutatyon düzeyleri ile katalaz ve glutatyon peroksidaz enzim aktiviteleri spektrofotometrik olarak belirlendi.

Bulgular: Tirozol ön tedavisinin doksorubisinin neden olduğu kalp dokusu malondialdehit düzeyindeki artışı ($p<0.05$), redükte glutatyon düzeyi ve glutatyon peroksidaz enzim aktivitesindeki azalmaları engellediği ve doksorubisinin kalp dokusunda meydana getirdiği oksidatif stresi baskıladığı görüldü. Kalp dokusu katalaz enzim aktiviteleri açısından gruplar arasında farklılık gözlenmedi. Kalpteki oksidatif hasarın azalmasına bağlı olarak serum kreatin kinaz MB ve kreatin kinaz aktivitelerinin önemli oranda azaldığı ($p<0.05$) tespit edildi. Ayrıca tirozol ön tedavisinin doksorubisinin kalp dokusunda meydana getirdiği histopatolojik lezyonları engellediği belirlendi.

Öneri: Tirozol uygulamasının doksorubisinin neden olduğu kardiyotoksisiteyi azaltabileceği düşünülmektedir.

Anahtar kelimeler: Kardiyotoksisite, doksorubisin, tirozol

Abstract

Aim: In this study, it was aimed to investigate the efficacy of tyrosol on cardiotoxicity induced by doxorubicin.

Materials and Methods: Rats were divided into 4 groups and each group included 8 rats. Groups 1 and 2 were given 1 ml of physiological saline, while groups 3 and 4 were given 20 mg/kg of tyrosol. In saline and tyrosol administrations, the oral gavage method was used. In addition, a single dose of 15 mg/kg dose of doxorubicin was administered intraperitoneally to group 2 and group 4 on the 12th day of the trial. On the 14th day of the experiment, serum and tissue samples were taken from the anesthetized rats and then euthanized. Serum creatine kinase MB and creatine kinase activities were analyzed. Heart tissues were extracted, and histological and oxidative stress characteristics were measured in these tissues. Heart tissue malondialdehyde and reduced glutathione levels, catalase and glutathione peroxidase activities were assessed spectrophotometrically.

Results: Tyrosol pretreatment inhibited doxorubicin-induced increase in heart tissue malondialdehyde level ($p<0.05$), the decrease in reduced glutathione level and glutathione peroxidase enzyme activity, and suppressed doxorubicin-induced oxidative stress in the heart tissue. In terms of cardiac tissue catalase enzyme activity, no differences were found between the groups. Because of the reduction in oxidative damage in the heart, the serum creatine kinase MB and creatine kinase activity decreased dramatically ($p<0.05$). Furthermore, it was discovered that tyrosol pretreatment reduced the histopathological lesions caused by doxorubicin in cardiac tissue.

Conclusion: It is thought that the administration of tyrosol may reduce the cardiotoxicity caused by doxorubicin.

Keywords: Cardiotoxicity, doxorubicin, tyrosol

Introduction

Doxorubicin, a member of the anthracycline drug group, is used to treat diseases such as leukemia, lymphoma, breast cancer, multiple myeloma, and lung cancer (Shaker et al 2018). Although it is an efficient anticancer drug, its usage is restricted because of its adverse effects on the heart, kidney, liver, ovary, and uterus (Granados Principal et al 2010, Jadhav et al 2013, Barıs et al 2019). Doxorubicin administration may cause cardiotoxicity, especially (Granados Principal et al 2010). It may cause some cardiovascular disorders such as tachycardia, arrhythmia, hypotension, dilated cardiomyopathy and cardiac dysfunction in cancer patients (An et al 2009, Ibrahim et al 2017, McGowan et al 2017). Cardiotoxicity may also develop after single dose or cumulative dose administration (Uygur et al 2014). The pathogenesis of cardiotoxicity caused by doxorubicin has not been fully elucidated. Oxidative stress is important in the pathogenesis of doxorubicin cardiotoxicity, including the formation of iron-dependent free oxygen radicals and peroxidation of lipids in the myocardial mitochondrial membrane, which causes suppression of DNA, RNA and proteins (Thomas 2017). It has been reported that other factors such as inflammation, apoptotic cell death of cardiomyocytes, mitochondrial dysfunction, myofibril degeneration and calcium usage altered by the sarcoplasmic reticulum may be effective in the pathogenesis of cardiotoxicity (Wouters et al 2005, Gandhi et al 2013, Mantawy et al 2014, Pecoraro et al 2018). The increase in free radicals in the myocardium and the decrease in the activity of endogenous antioxidants have an important role in the pathogenesis of heart failure caused by doxorubicin (Lódi et al 2019).

Tyrosol (2-(4-hydroxyphenyl) ethanol), a phenolic compound, is found in olive oil and wine (Bu et al 2007, Thibault et al 2011). Many studies have proven that Tyrosol has antioxidant (Bu et al 2007, Thibault et al 2011, Guvenc et al 2019), anti-inflammatory (Kima et al 2017), antihyperlipidemic (Chandramohan and Pari 2021), neuroprotective, anti-apoptotic and anticancer effects (Plotnikov and Plotnikova 2021).

In this study, it was aimed to investigate the protective efficacy of tyrosol on cardiotoxicity induced by doxorubucin.

Material and Methods

Animal material

32 Wistar albino female rats weighing 180-250 g were used in the study. Experimental animals were housed in accordance with the care and use conditions of laboratory animals (12 hours light, 12 hours dark and 21±1°C). The rats were given standard commercial feed (pellet feed) and water ad libitum.

Experimental groups

The cardiotoxicity model with doxorubicin in rats was established based on the article by Ikewuchi et al (2021), and the dose of tyrosol in rats was calculated based on the article by Cellat et al (2021). The experimental groups of the study consisted of four groups: Group 1 (Control group), group 2 (Doxorubicin), group 3 (Tyrosol) and group 4 (Doxorubicin + Tyrosol). Each group consisted of 8 rats and a total of 32 female rats were used. For 14 days, rats in Groups 1 and 2 were given 1 ml of saline once a day. The rats in groups 3 and 4 were given tyrosol at a dose of 20 mg/kg in 1 ml of physiological saline once a day also for 14 days. Oral gavage method was used in saline and tyrosol applications. Also, on the 12th day of the experiment, the rats in groups 2 and 4 were intraperitoneally injected with doxorubicin at a concentration of 15 mg/kg (Ikewuchi et al 2021). On the 14th day of the experiment, blood samples were taken from the tail veins of the rats under ketamine (60 mg/kg IM) + xylazine (10 mg/kg IM) anesthesia to serum tubes, and then they were euthanized using the decapitation method. Then hearts of the euthanized rats were removed. The tissue samples were examined for histopathological and oxidative stress markers. The heart tissue samples removed for histopathological analysis were kept in 10% buffered formalin and stored until further analysis. The remaining tissue samples were kept in deep freezer (-80 ºC) for oxidative parameter analysis.

Measurement of serum CK and CK-MB enzyme activities

Blood samples were centrifuged at 3000 rpm for 15 minutes, their serum was removed and placed in eppendorf tubes. Creatine kinase (CK) and creatine kinase MB (CK-MB) activity levels were analyzed in fresh serum samples. Gesan brand automatic biochemistry analyzer device was used in the analysis process.

Analysis of oxidant and antioxidant parameters in heart tissue

The concentration of thiobarbituric acid reagents and the level of lipid peroxidation were measured. The malondialdehyde (MDA) level, which was used as a lipid peroxidation index, was determined according to the method reported by Placer et al (1966) and was expressed as nanomoles per gram of protein. The reduced glutathione (GSH) level was measured according to the method reported by Sedlak and Lindsay (1968) and expressed as nanomoles per gram of protein. Glutathione peroxidase (GSH-Px, EC 1.11.1.9) enzyme activity analysis was performed according to the method reported by Lawrence and Burk

(1976). Activity findings were expressed in international units per gram of protein. The method reported by Aebi (1983) was used for the determination of catalase (CAT, EC 1.1.11.16) enzyme activity. Activity results were expressed as ku/protein. Protein analysis was performed based on the method of Lowry et al (1951).

Histopathological analysis

At the end of the experiment, all rats were euthanized under anesthesia and their heart tissues were removed. Some of the heart tissue samples were separated for the analysis of oxidant and antioxidant parameters and stored in a deep freezer (-80 °C). Tissue samples separated for histopathological analysis were fixed in 10% buffered formaldehyde solution for 48 hours. They became transparent by passing through a series of xylene. Next, the samples were blocked in paraffin and sectioned at 5 µm thicknesses by rotary microtome (Leica, RM 2135). After that, the slides were stained with hematoxylin and eosin (H&E) for histopathological evaluation (Luna 1968). All slides were examined and microphotographed by using light microscope (Olympus BX50-F4, Tokyo, Japan) with imaging system (Olympus DP12-BSW, Tokyo, Japan) for detection of lesions in the brain.

Statistical analysis

Using Shapiro-Wilk normality analysis in the data obtained in the study, it was evaluated whether the values of the groups had a normal distribution. As a result of the analysis, it was seen that the values of all parameters had normal distribution. One-way analysis of variance (ANOVA) was used to compare group means. In addition, differences between groups were determined using the Tukey test. IBM SPSS Statistics 23 package program was used for statistical analysis and ($p<0.05$) was considered statistically significant.

Results

Statistically significant increases were observed in serum CK and CK-MB enzyme activities of rats in the doxorubicin group ($p<0.05$). There was no significant difference between the control and tyrosol groups in terms of both parameters. When the serum CK and CK-MB activities of the rats in the group receiving doxorubicin plus tyrosol and in the group administered only doxorubicin were compared, it was determined that there were statistically significant decreases ($p<0.05$). These reductions were thought to be linked to tyrosol's antioxidant activity, which could mean less oxidative damage in heart tissue. Table 1 summarizes the findings for these parameters.

In this investigation, doxorubicin administration significantly increased MDA levels in cardiac tissue while lowering GSH levels and GSH-Px enzyme activity ($p<0.05$). The activity of the CAT enzyme did not differ significantly between the groups ($p>0.05$). In terms of MDA and GSH levels, as well as CAT and GSH-Px enzyme activity, there was no statistical difference between the control and tyrosol groups. While a significant decrease in heart tissue MDA level was determined in rats given doxorubicin plus tyrosol

Table 1. Serum CK and CK-MB enzyme activity levels

Group/Parameter	CK (U/L)	CK-MB (U/L)
Control	863.07±237.24^{b}	895.03±95.01^{c}
Doxorubicin	1482.08±93.46^{a}	1581.58±62.55^{a}
Tyrosol	836.71±119.94^{b}	876.97±65.43^{c}
Doxorubicin + Tyrosol	960.89±286.56^{b}	1143.53±96.75^{b}

$^{a,b,c;}$ Varied characters in the same column are statistically different ($p<0.05$). CK, creatine kinase; CK-MB, creatine kinase MB

Table 2. Heart tissue MDA and GSH levels and GSH-Px and CAT enzyme activities

Group/Parameter	MDA (nmol/g prot)	GSH (nmol/g prot)	GSH-Px (IU/gr prot)	CAT (KU/g prot)
Control	7.83±1.16^{bc}	1.11±0.17^{a}	47.87±9.90^{a}	31.63±3.81
Doxorubicin	11.92±2.05^{a}	0.87±0.14^{b}	38.94±4.96^{b}	28.43±8.37
Tyrosol	7.18±0.84^{c}	1.16±0.18^{a}	48.85±4.06^{a}	32.27±2.37
Doxorubicin + Tyrosol	9.40±1.50^{b}	1.01±0.19^{ab}	46.28±8.05^{ab}	30.30±2.89

$^{a,b,c;}$ Varied characters in the same column are statistically different ($p<0.05$). MDA, malondialdehyde; GSH, reduced glutathione; CAT, catalase; GSH-Px, glutathione peroxidase

($p<0.05$), the increase in GSH level and GSH-Px activity was not statistically significant. When these findings were examined, it was discovered that tyrosol has an antioxidant effect and it may alleviate the adverse effects of oxidative stress in cardiac tissue caused by doxorubicin. Table 2 shows the results of the oxidant and antioxidant parameters.

The examinations identified no macroscopic changes in any of the rat groups. The evaluation of heart tissue samples revealed that cardiac muscle cells in the control (Figure 1A) and tyrosol (Figure 1C) groups had normal histological features. Heart sections from the doxorubicin group rats showed mild to moderate degenerative and necrotic histopathological changes. Cardiomyocytes in this group showed hyaline degeneration, vacuolar degeneration (cytoplasmic vacuolization), and myocytolysis.

Cytoplasmic vacuoles were observed in the cytoplasm of cardiomyocytes as sharp-edged, non-staining spaces of varying sizes. The capillaries in several of the vessels were congested. In addition, some myocardial fibrils were disorganized as a result of degeneration. The transverse striations detected under a high magnification light microscope in these deteriorated heart muscle fibers disappeared with disorganization, according to the findings. Few inflammatory cells were seen between the muscle fibers once again. Some necrotic cells' nuclei were pycnotic and hyperchromatic, while others' nuclei had completely disappeared (Figure 1B). Only a slight congestion and a few hyaline degenerated myofibrils were identified in certain capillaries in the tyrosol with doxorubicin group. With the exception of minor histopathological changes, the rats in this group had near-normal cardiac muscle histology (Figure 1D). Figures 1A, B, C, and D show the histopathological findings of all groups.

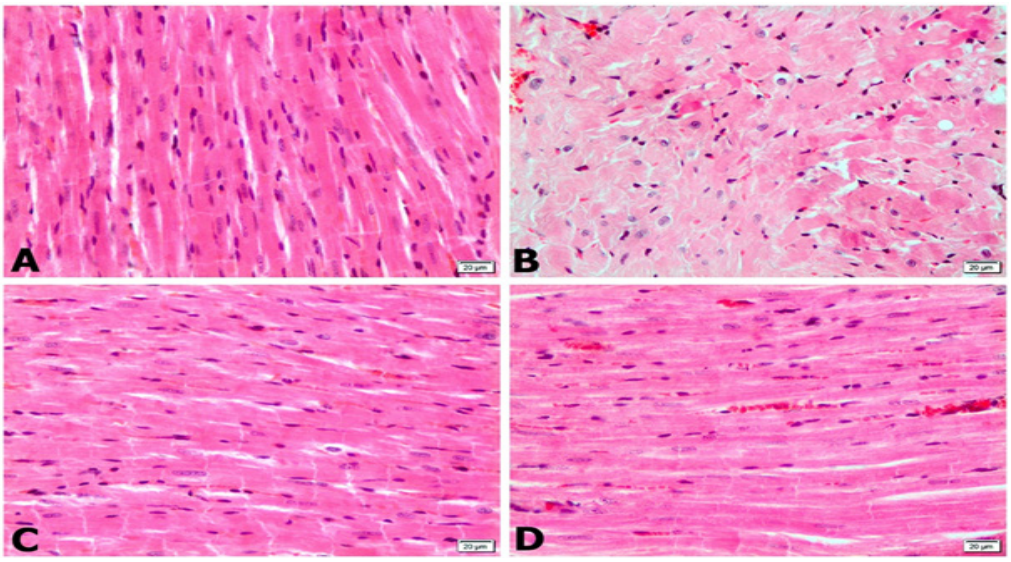

Figure 1. Histopathological view of heart tissue with H&E staining. Normal histological structure in the Control groups (A). Mild to moderate degenerative and necrotic changes in heart muscle in the Doxorubucin gruop (B). Normal histological appearance in the Tyrosol group (C). Mild degenerative changes in heart muscle Doxorubucin + Tyrosol group (D)

Discussion

Doxorubicin is an anthracycline group antibiotic used to treat a variety of cancers, including hematologic cancer, solid tumors, and soft tissue sarcomas, and can commonly cause heart failure and heart damage as a side effect (Pehlivan et al 2020). Doxorubicin causes serious morphological and functional cardiac changes and ultimately irreversible cardiomyopathy and heart failure (Gandhi et al 2013, Kim et al 2017, Guo et al 2018). According to Rašković et al (2011), doxorubicin causes cardiotoxicity by disrupting the balance between reactive oxygen species (ROS) and antioxidant enzyme levels. Oxidative stress and lipid peroxidation are the most important causes of doxorubicin-induced cardiotoxicity according to in vivo and in vitro investigations (Gandhi et al 2013). Due to the presence of cardiolipin in cardiac mitochondria, cardiomyocytes are significantly more vulnerable to oxidative stress (Tahover et al 2015, Giampieri et al 2016). Anionic cardiolipin found in the mitochondrial inner membrane has a high affinity for binding with the cationic drug doxorubucin. Therefore, mitochondria play an important role in doxorubicin-induced cardiotoxicity (Octavia et al 2012, Nebigil and Desaubry 2018). The nicotinamide adenine dinucleotide hydrogen dehydrogenase (NADH) enzyme in the mitochondria reacts with molecular oxygen to reduce doxorubicin to the semiquinone radical. Semiquinone plays a role in the formation of hydrogen peroxide, hydroxyl and superoxide radicals (Volkova and Russell 2012). Excessive ROS production causes cell damage and, consequently, increased lipid peroxidation and increased MDA production (Subbarao et al 2018). MDA is a stable lipid peroxidation end product that can be used to predict lipid peroxidation and tissue damage induced by free radicals (Xiao 2015). In many scientific studies, it has been reported that doxorubicin administration increases the level of heart tissue MDA in experimental animals (Haybara et al 2019, Zare et al 2019, Mohammeda et al 2020, Sandamali et al 2020, Sheibani et al 2020, Ahmed et al 2021, Ikewuchi et al 2021). The heart tissue MDA level of the rats in the doxorubicin-only group increased considerably as compared to the control group in this study. In an experimental asthma model established using ovalbumin tyrosol caused a decrease in lung tissue MDA level, an increase in GSH level and GSH-Px enzyme activity, had a strong antioxidant effect, and prevented lung damage. According to the same study, tyrosol had no effect on catalase enzyme activity in lung tissue (Cellat et al 2021). In a dextran sulfate sodium (DSS)-induced ulcerative colitis model in rats, tryrosol lowered the MDA value of the colon tissue, increased the GSH level, CAT, and GSH-Px enzyme activities to levels similar to the control group, and protected the colon tissue from ulcerative colitis (Guvenc et al 2019). The cardiac tissue MDA levels of the rats in the group given tyrosol and doxorubicin showed statistically significant reduction in this investigation. The difference between the control and tyrosol groups was not significant. GSH, an intracellular hydrophilic antioxidant, protects cells from free radical damage (Pandey and Rizvi 2010). It has been reported that the amount of GSH in the heart tissue decreased significantly in rats given doxorubicin (Haybara et al 2019, Zare et al 2019, Alanazi et al 2020, Mohammeda et al 2020, Sandamali et al 2020, Sheibani et al 2020, Ahmed et al 2021, Ikewuchi et al 2021). The GSH level in heart tissue was shown to be lower in the doxorubicin group in this investigation. The results related to GSH are consistent with what has been published in the literature. There is additional imformation that doxorubicin treatment raises GSH levels in cardiac tissue (Zare et al 2019). The inconsistency with the GSH finding of this study could be due to variances in the dose and duration of doxorubicin administration. The tissue GSH levels of rats in the control and tyrosol groups did not differ significantly. The cardiac tissue GSH level in rats given doxorubicin and tyrosol was found to be similar to that of the control group.

Antioxidant enzymes such as GSH-Px and CAT protect the body against tissue damage caused by oxidative stress (Afsar et al 2017). Doxorubicin causes decreases in the activities of antioxidant enzymes such as CAT and superoxide dismutase (SOD). Because cardiac tissues have less antioxidant reserve than other organs in the body, they are more vulnerable to doxorubicin damage (Halestrap 2006). The hydrogen peroxide formed in the heart tissue as a result of doxorubicin's effect is converted into water and molecular oxygen by the enzyme catalase. Therefore, increased ROS generation during doxorubicin treatment lowers the level of catalase, reducing cardiomyocytes' ability to detoxify ROS (Afsar et al 2017, Bhatt and Joshi 2017). Doxorubicin decreases cardiac tissue catalase enzyme activity according to a substantial body of literature (Zhang et al 2017, Haybara et al 2019, Wu et al 2019, Birari et al 2020, Li et al 2020, Sandamali et al 2020, Ikewuchi et al 2021). Some researchers, however, suggested that doxorubicin treatment had no effect on heart tissue catalase activity (Al Taee et al 2019). When comparing the doxorubicin group to the control group, it was discovered that the CAT enzyme activity of the doxorubicin group caused a decrease in CAT activity, however this decline was not statistically significant. In terms of CAT enzyme activity, there was no statistically significant difference between the groups. Our findings on CAT enzyme activity are in agreement with those of Al-Taee et al (2019). It was thought that the inconsistency with other literature might be due to the application time and dose of doxorubicin. GSH-Px acts as a catalyst in the reaction of hydroperoxidase with GSH (Sumitra et al 2001). Doxorubicin treatment has been shown to cause statistically significant decreases in GSH-Px enzyme activity in cardiac tissue (Zhang et al 2017, Zhao et al 2018, Haybara et al 2019, Öner et al 2019, Wu et al 2019, Li et al 2020, Sandamali et al 2020, Ikewuchi et al 2021). There is additional evidence in the literature that the

same application has no effect on the activity of the GSH-Px enzyme in cardiac tissue (Kumrala et al 2015). The amount of GSH-Px enzyme activity in cardiac tissue was shown to be considerably decreased after doxorubicin administration in this investigation. There was no statistically significant difference between the control and tyrosol groups. There were increases in cardiac tissue GSH-Px enzyme activity in the group receiving tyrosol and doxorubicin, but these increases were not statistically significant. When the oxidant and antioxidant parameters of heart tissue were analyzed in the study, it was found that tyrosol had an antioxidant effect and as a result it could alleviate oxidative stress in the heart tissue caused by doxorubicin.

CK is one of the specific and sensitive markers of cardiac muscle damage (Asiri 2010). CK-MB is normally present in the cellular compartment, but with myocardial damage, it leaks into the circulation due to the breakdown of contractile components and the sarcoplasmic reticulum (Akila and Vennila 2016). It has been stated that doxorubicin produces a rise in the release of enzymes like CK, which is caused by the activation of lipid peroxidation in cardiac membranes (Saad et al 2001). The significant increase in serum CK and CK-MB levels after doxorubicin treatment is due to increased lipid peroxidation and oxidative stress in heart tissue (Ammar et al 2013). In many scientific studies, it is emphasized that doxorubicin administration causes significant increases in serum CK (Haybara et al 2019, Li et al 2020, Liao et al 2020, Yuan et al 2020, Ahmed et al 2021, Ikewuchi et al 2021, Wan et al 2021) and CK-MB (Al Taee et al 2019, Zare et al 2019, Alanazi et al 2020, Li et al 2020, Liao et al 2020, Sheibani et al 2020, Tiana et al 2020, Yuan et al 2020, Zhang et al 2020, Ikewuchi et al 2021, Wan et al 2021) levels in experimental animals. In this study, it was discovered that rats receiving only doxorubicin had statistically significant increases in serum CK and CK-MB levels. There was no difference between the control and tyrosol groups. Serum CK and CK-MB levels were found to be significantly lower in the group that received tyrosol in addition to doxorubicin. These decreases were thought to be due to tyrosol's antioxidant effect on heart tissue, which inhibits lipid peroxidation.

Doxorubicin administration causes various histopathological changes, such as cardiomyocyte vacuolization in heart tissue, increased extracellular fibrosis, muscle fiber disorder, myofibril loss, enlarged and abnormally shaped mitochondria, inflammatory cell infiltration, increased cell death, cardiomyocyte apoptosis, edema of myocardial cells, myocardial tissue hemorrhage, blood vessel occlusion, pycnotic nuclei and necrosis (Kumrala et al 2015, Haybara et al 2019, Ma et al 2019, Öner et al 2019, Liao et al 2020, Sandamali et al 2020, Tiana et al 2020, Yuan et al 2020, Ahmed et al 2021, Wan et al 2021). When the heart tissue samples from the control and tyrosol groups were examined, the cardiac muscle cells were found to have normal histological features. Degenerative and necrotic histopathological changes ranging from mild to moderate, such as hyaline degeneration of cardiomyocytes in some areas, vacuolar degeneration (cytoplasmic vacuolization), myocytolysis, congestion in capillaries, loss of transverse striations in degenerated heart muscle fibrils, sporadic infiltration of inflammatory cells between muscle fibers, pycnotic and hyperchromatic appearance of the nuclei of some necrotic cells, and complete disappearance of the nuclei of some cells were detected in the heart tissue of the rats in the doxorubicin group. The histology of heart tissue in the group given tyrosol and doxorubicin was mostly close to normal, with the exception of histopathological changes, such as very minor congestion in certain capillaries and a few myofibrils with hyaline degeneration. The biochemical and histological findings revealed that tyrosol pretreatment protected against doxorubicin-induced cardiotoxicity.

Conclusion

Pre-treatment with tyrosol reduced cardiotoxicity, which is the most serious side effect of doxorubicin. In order to better elucidate the effect of tyrosol on the cardiotoxicity of doxorubicin, new studies at the molecular level are needed on different doses and durations of use of tyrosol.

Acknowledgement

We would like to thank Dr. Tuncer Kutlu, faculty member of HMKU, Faculty of Veterinary Medicine Department of Pathology, who contributed to our research with the histopathological analysis.

Conflict of Interest

The authors did not report any conflict of interest or financial support.

Funding

During this study, any pharmaceutical company which has a direct connection with the research subject, a company that provides and / or manufactures medical instruments, equipment and materials or any commercial company may have a negative impact on the decision to be made during the evaluation process of the study or no moral support.

References

Aebi HI, 1983. Methods of enzymatic analysis. Catalase, 673-686.

Afsar T, Razak S, Batoo KM, Khan MR, 2017. Acacia hydaspica R. Parker prevents doxorubicin-induced cardiac injury by attenuation of oxidative stress and structural

cardiomyocyte alterations in rats. BMC Complement Altern Med, 17(1), 1-14.

Ahmed AZ, Satyam SM, Shetty P, D'Souza MR, 2021. Methyl gallate attenuates doxorubicin-induced cardiotoxicityin rats by suppressing oxidative stress. Scientifica, 2021,12.

Akila P, Vennila L, 2016. Chlorogenic acid a dietary polyphenol attenuates isoproterenol induced myocardial oxidative stress in rat myocardium: An in vivo study. Biomed Pharmacother, 84, 208–214.

Alanazi AM, Fadda L, Alhusaini A, Ahmad R, et al., 2020. Liposomal resveratrol and/or carvedilol attenuate doxorubicin-induced cardiotoxicity by modulating inflammation, oxidative stress and S100A1 in rats. Antioxidants, 9(2), 159.

Al-Taee H, Azimullah S, Meeran MFN, Almheiri MKA, et al., 2019. β-caryophyllene, a dietary phytocannabinoid attenuates oxidative stress, inflammation, apoptosis and prevents structural alterations of the myocardium against doxorubicin-induced acute cardiotoxicity in rats: An in vitro and in vivo study. Eur J Pharmacol, 858, 172467.

Ammar ESM, Said SA, El-Damarawy SL, Suddek GM, 2013. Cardioprotective effect of grape-seed proanthocyanidins on doxorubicin-induced cardiac toxicity in rats. Pharm Biol, 51(3), 339–344.

An JF, Li PF, Li JC, Dietz R, et al., 2009. ARC is a critical cardiomyocyte survival switch in doxorubicin cardiotoxicity. J Mol Med-Jmm, 87 (4), 401–410.

Asiri YA, 2010. Probucol attenuates cyclophosphamide induced oxidative apoptosis, p53 and Bax signal expression in rat cardiac tissues. Oxid Med Cell Longev, 3, 308-316.

Barış VO, Gedikli E, Yersal N, Müftüoğlu S, et al., 2019. Protective effect of taurine against doxorubicin-induced cardiotoxicity in rats: Echocardiographical and histological findings, Amino acids. Amino Acids, 51, 649–1655.

Bhatt L, Joshi V, 2017. *Mangifera indica* L. leaf extract alleviates doxorubicin induced cardiac stress. J Intercult Ethnopharmacol, 6(3), 284–289.

Birari L, Wagh S, Patil KR, Mahajan UB, et al., 2020. Aloin alleviates doxorubicin induced cardiotoxicity in rats by abrogating oxidative stress and pro inflammatory cytokines. Cancer Chemother Pharmacol, 86, 419–426.

Bu Y, Rho S, Kim J, Kim MY, et al., 2007. Neuroprotective effect of tyrosol on transient focal cerebral ischemia in rats. Neurosci Lett, 414, 218–221.

Cellat M, Kuzu M, İşler CT, Etyemez M, et al., 2021. Tyrosol improves ovalbumin (OVA) induced asthma in rat model through prevention of airway inflammation. Naunyn Schmiedebergs Arch Pharmacol, 394(10), 2061-2075.

Chandramohan R, Pari L, 2021. Antihyperlipidemic effect of tyrosol, a phenolic compound in streptozotocin-induced diabetic rats. Toxicol Mech Methods, 31(7), 507-516.

Gandhi H, Patel VB, Mistry N, Patni N, et al., 2013. Doxorubicin mediated cardiotoxicity in rats: protective role of felodipine on cardiac indices. Environ Toxicol Pharmacol, 36(3), 787–795.

Giampieri F, Alvarez-Suarez JM, Gasparrini M, Forbes-Hernandez TY, et al., 2016. Strawberry consumption alleviates doxorubicin-induced toxicity by suppressing oxidative stress. Food Chem Toxicol, 94, 128–137.

Granados-Principal S, Quiles JL, Ramirez-Tortosa CL, Sanchez-Rovira P, et al., 2010. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. Food Chem Toxicol, 48, 1425–1438.

Guo R, Hua Y, Ren J, Bornfeldt KE, et al., 2018. Cardiomyocyte-specific disruption of cathepsin K protects against doxorubicin-induced cardiotoxicity. Cell Death Dis, 9(6), 692.

Güvenç M, Cellat M, Özkan H, Tekeli İO, et al., 2019. Protective effects of tyrosol against DSS-induced ulcerative colitis in rats. Inflammation, 42, 1680–1691.

Halestrap AP, 2006. Calcium, mitochondria and reperfusion injury: a pore way to die. Biochem Soc Trans, 34, 232–237.

Haybara H, Goudarzi M, Mehrzadi S, Aminzadeh A, et al., 2019. Effect of gemfibrozil on cardiotoxicity induced by doxorubicin in male experimental rats. Biomed Pharmacother, 109, 530–535.

Ibrahim DM, Radwan RR, Abdel Fattah SM, 2017. Antioxidant and antiapoptotic effects of sea cucumber and valsartan against doxorubicin-induced cardiotoxicity in rats: The role of low dose gamma irradiation. J Photochem Photobiol, B 170, 70–78.

Ikewuchi JC, Ikewuchi CC, Ifeanacho MO, Jaja VS, et al., 2021. Attenuation of doxorubicin-induced cardiotoxicity in Wistar rats by aqueous leaf-extracts of *Chromolaena odorata* and *Tridax procumbens*. J Ethnopharmacol, 274, 114004.

Jadhav VB, Thakare VN, Suralkar AA, Naik SR, 2013. Ameliorative effect of *Luffa acutangula* Roxb. on doxorubicin induced cardiac and nephrotoxicity in mice. IJEB, 52(02), 149-156.

Kim SH, Kim KJ, Kim JH, Kwak JH, et al., 2017. Comparision of doxorubicin induced cardiotoxicity in the ICR mice of different sources. Lab Anim Res, 33(2), 165–170.

Kima YY, Leeb S, Kima MJ, Kanga BC, et al., 2017. Tyrosol attenuates lipopolysaccharide-induced acute lung injury by inhibiting the inflammatory response and maintaining the alveolar capillary barrier. Food Chem Toxicol, 109, 526–533.

Kumrala A, Giris M, Soluk-Tekkes M, Olgac V, et al., 2015. Effect of olive leaf extract treatment on doxorubicin-induced cardiac, hepatic and renal toxicity in rats. Pathophysiology, 22, 117–123.

Lawrence RA, Burk RF, 1976. Glutathione peroxidase activity in selenium-deficient rat liver. Biochem Biophys Res Commun, 71, 952-958.

Li H, Xia B, Chen W, Zhang Y, et al., 2020. Nimbolide prevents myocardial damage by regulating cardiac biomarkers, antioxidant level, and apoptosis signaling against doxorubicin-induced cardiotoxicity in rats. J Biochem Mol Toxicol, e22543.

Liao D, Zhang C, Liu N, Cao L, et al., 2020. Involvement of neurotrophic signaling in doxorubicin induced cardiotoxicity. Exp Ther Med, 19, 1129-1135.

Lódi M, Priksz D, Fülöp GÁ, 2019. Advantages of prophylactic

versus conventionally scheduled heart failure therapy in an experimental model of doxorubicin-induced cardiomyopathy. J Transl Med, 17, 1–16.

Lowry OH, Rosebrough NJ, Farr AL, Randall RJ, 1951. Protein measurement with the folin phenol reagent. J Biol Chem, 193, 265-275.

Luna LG, 1968. Manuel of histologic staining methods of the armed forces institute of pathology. McGraw-Hill Book Co, Newyork, p- 32.

Ma T, Kandhare AD, Mukherjee Kandhare AA, Bodhankar SL, 2019. Fisetin, a plant flavonoid ameliorates doxorubicin-induced cardiotoxicity in experimental rats: the decisive role of caspase-3, COXII, cTn-I, iNOs and TNF-α. Mol Biol Rep, 46, 105–118.

Mantawy EM, El-Bakly WM, Esmat A, Badr AM, et al., 2014. Chrysin alleviates acute doxorubicin cardiotoxicity in rats via suppression of oxidative stress, inflammation and apoptosis. Eur J Pharmacol, 728, 107–118.

McGowan JV, Chung R, Maulik A, Piotrowska I, et al., 2017. Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther, 31 (1), 63–75.

Mohammeda HS, Hosny EN, Khadrawy YA, Magdy M, et al., 2020. Protective effect of curcumin nanoparticles against cardiotoxicity induced by doxorubicin in rat. Biochim Biophys Acta, 1866(5), 165665.

Nebigil CG, D´esaubry L, 2018. Updates in anthracycline mediated cardiotoxicity. Front Pharmacol, 9.

Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, et al., 2012. Doxorubicin-induced cardiomyopathy: From molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol, 52, 1213–1225.

Oner Z, Altınoz E, Elbe H, Ekinci N, 2019. The protective and therapeutic effects of linalool against doxorubicin-induced cardiotoxicity in wistar albino rats. Hum Exp Toxicol, 38(7), 803-813.

Pandey KB, Rizvi SI, 2010. Markers of oxidative stress in erythrocytes and plasma during aging in humans. Oxid Med Cell Longev, 3(1), 2–12.

Pecoraro M, Ciccarelli M, Fiordelisi A, Iaccarino G, et al., 2018. Diazoxide improves mitochondrial connexin 43 expression in a mouse model of doxorubicin-induced cardiotoxicity. Int J Mol Sci, 19(3), 757.

Pehlivan DY, Durdagi G, Oyar EO, Akyol S, et al., 2020. The effects of melatonin and thymoquinone on doxorubicin-induced cardiotoxicity in rats. Bratisl Med J, 121(10), 753-759.

Placer ZA, Cushman LL, Johnson BC, 1966. Estimation of product of lipid peroxidation (malonyldialdehyde) in biochemical systems. Anal Biochem, 16(2), 359–364.

Plotnikov MB, Plotnikova TM, 2021. Tyrosol as a neuroprotector: Strong effects of a “Weak” antioxidant. Curr Neuropharmacol, 19, 434-448.

Rašković A, Stilinović N, Kolarović J, Vasović V, et al., 2011. The protective effects of silymarin against doxorubicin-induced cardiotoxicity and hepatotoxicity in rats. Molecules, 16(10), 8601–8613.

Saad SY, Najjar TA, Al-Rikabi AC, 2001. The preventive role of deferoxamine against acute doxorubicin-induced cardiac, renal and hepatic toxicity in rats. Pharmacol Res, 43, 211–218.

Sandamali JAN, Hewawasam RP, Jayatilaka KAPW, Mudduwa LKB, 2020. Cardioprotective potential of *Murraya koenigii* (L.) spreng. leaf extract against doxorubicin-induced cardiotoxicity in rats. eCAM, 2020, 16.

Sedlak J, Lindsay RH, 1968. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman’s reagent. Anal Biochem, 25, 192-205.

Shaker RA, Abboud SH, Assad HC, Hadi N, 2018. Enoxaparin attenuates doxorubicin induced cardiotoxicity in rats via interfering with oxidative stress, inflammation and apoptosis. BMC Pharmacol Toxicol, 19.

Sheibani M, Nezamoleslami S, Ghanesefat HF, Emami AH, et al., 2020. Cardioprotective effects of dapsone against doxorubicin induced cardiotoxicity in rats. Cancer Chemother Pharmacol, 85, 563–571.

Subbarao R, Ok SH, Lee S, Kang D, et al., 2018. Lipid emulsion inhibits the late apoptosis/cardiotoxicity induced by doxorubicin in rat cardiomyoblasts. Cells, 7(10), 144.

Sumitra M, Manikandan P, Kumar DA, Arutselvan N, et al., 2001. Experimental myocardial necrosis in rats: role of arjunolic acid on platelet aggregation, coagulation and antioxidant status. Mol Cell Biochem, 224 (1), 135–142.

Tahover E, Patil YP, Gabizon AA, 2015. Emerging delivery systems to reduce doxorubicin cardiotoxicity and improve therapeutic index: Focus on liposomes. Anticancer Drugs, 26(3), 241–258.

Thibault SLC, Arseneault M, Longpre F, Ramassamy C, 2011. Tyrosol and hydroxytyrosol, two main components of olive oil, protect N2a cells against amyloid-b-induced toxicity. Involvement of the NF-kB signaling. Curr Alzheimer Res, 8, 543–551.

Thomas, SA, 2017. Chemotherapy agents that cause cardiotoxicity. US Pharm, 42(9), 24-33.

Tiana W, Yang L, Liu Y, He J, et al., 2020. Resveratrol attenuates doxorubicin-induced cardiotoxicity in rats by up-regulation of vascular endothelial growth factor B. J Nutr Biochem, 79, 108132.

Uygur R, Aktas C, Tulubas F, Alpsoy S, et al., 2014. Cardioprotective effects of fish omega-3 fatty acids on doxorubicin-induced cardiotoxicity in rats. Hum Exp Toxicol, 33(4), 435–445.

Volkova M, Russell R, 2012. Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. Curr Cardiol Rev, 7(4), 214–220.

Wan Y, Hea B, Zhu D, Wang L, et al., 2021. Nicotinamide mononucleotide attenuates doxorubicin-induced cardiotoxicity by reducing oxidative stress, inflammation and apoptosis in rats. Arch Biochem Biophys, 712, 109050.

Wouters KA, Kremer LC, Miller TL, Herman EH, et al., 2005. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. Br J Haematol, 131 (5), 561–578.

Wu YZ, Zhang L, Wu ZX, Shan TT, et al., 2019. Berberine

ameliorates doxorubicin-induced cardiotoxicity via a SIRT1/p66Shc-mediated pathway. Oxid Med Cell Longev, 2019, 14.

Xiao NN, 2015. Effects of resveratrol supplementation on oxidative damage and lipid peroxidation induced by strenuous exercise in rats. Biomol Ther, 23(4), 374–378.

Yuan Y, Fan S, Shu L, Huang W, et al., 2020. Exploration the mechanism of doxorubicin-induced heart failure in rats by integration of proteomics and metabolomics data. Front Pharmacol, 11, 600561.

Zare MFR, Rakhshan K, Aboutaleb N, Nikbakht F, et al., 2019. Apigenin attenuates doxorubicin induced cardiotoxicity via reducing oxidative stress and apoptosis in male rats. Life Sci, 232, 116623.

Zhang YD, Ma CY, Liu CS, Wei F, 2020. Luteolin attenuates doxorubicin-induced cardiotoxicity by modulating the PHLPP1/AKT/Bcl-2 signalling pathway. Peer J, 8, e8845.

Zhang YY, Yib M, Huang Y, 2017. Oxymatrine ameliorates doxorubicin induced cardiotoxicity in rats. Cell Physiol Biochem, 43, 626-635.

Zhao L, Tao X, Qi Y, Xu L, et al., 2018. Protective effect of dioscin against doxorubicin-induced cardiotoxicity via adjusting microRNA-140-5p-mediated myocardial oxidative stress. Redox Biol, 16, 189–198.

Author Contributions

Motivation / Concept: Mustafa Cellat, Muhammed Etyemez
Design: Mustafa Cellat, Muhammed Etyemez
Control/Supervision: Mustafa Cellat, Muhammed Etyemez
Data Collection and/or Processing: Mustafa Cellat, Muhammed Etyemez
Analysis and / or Interpretation: Mustafa Cellat, Muhammed Etyemez
Literature Review: Mustafa Cellat, Muhammed Etyemez
Writing the Article: Mustafa Cellat, Muhammed Etyemez
Critical Review: Mustafa Cellat, Muhammed Etyemez

Ethical Approval

The presented study was carried out with the approval and permission of Hatay Mustafa Kemal University Animal Experiments Local Ethics Committee with the decision numbered 2021/07-01 dated 31.12.2021.

CITE THIS ARTICLE: *Cellat M, Etyemez M, 2022. Investigation of the efficacy of tyrosol on doxorubicin-induced acute cardiotoxicity in rats. Eurasian J Vet Sci, 38, 3, 159-167.*